Potential role of statins on wound healing: review of the literature

Shadi Farsaei, Hossein Khalili, Effat Sadat Farboud

Farsaei S, Khalili H, Farboud ES. Potential role of statins on wound healing: review of the literature. Int Wound J 2012; 9:238–247

ABSTRACT

Wound healing is a dynamic and complex biological process, which requires coordinated events including haemostasis, inflammation, proliferation, revascularisation and remodelling. Impaired wound healing is a common problem that occurs in both community and hospital settings. Various experimental and clinical studies have evaluated different modalities for the treatment of topical wounds, such as sugar, antibiotics, honey and phytotherapies; also statins have diverse pleiotropic effects that have been suggested to be useful to improve wound healing. Data derived from both animal and human studies showed that statins especially atorvastatin, simvastatin and pravastatin can accelerate the wound-healing process. However, further high-quality and evidence-based studies are needed to address the best statin drug, appropriate dose, the best administration route, duration of treatment and to determine correlation between pleiotropic effects of statins and their probable clinical benefits.

Key words: Statin • Wound healing

Key Points

- inflammation is one of the important causes of delayed wound healing because of oxidative stress, proteolysis and accumulation of toxic substances that occur during inflammation
- in addition, bacterial infection has a detrimental effect on the wound healing process by impeding angiogenesis and secretion of plasminogen activator and proteolytic enzymes
- recent studies showed that statins have a crucial role in the regulation of angiogenesis
- it was shown that simvastatin could increase VEGF synthesis and release at the wound site which is a crucial event for new blood vessels' production and subsequently ameliorates impaired wound healing in diabetic mice

INTRODUCTION

The healing of open skin wounds is a dynamic and complex biological process that includes different coordinated events such as haemostasis, inflammation, proliferation, revascularisation and remodelling (1–3). Inflammation is one of the important causes of delayed wound healing because of oxidative stress, proteolysis and accumulation of toxic substances that occur during inflammation (4). In addition, bacterial infection has a detrimental effect on the wound-healing process by impeding angiogenesis and secretion of plasminogen activator and proteolytic enzymes (5).

Authors: S Farsaei, Pharm D, Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran; H Khalili, Pharm D, Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran; ES Farboud, Pharm D, Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Address for correspondence: Dr H Khalili, Pharm D, Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

E-mail: khalilih@tums.ac.ir

Different studies have described high prevalence of chronic wounds and have showed impaired wound healing as a common problem in both community and hospital settings (6,7).

Pre-existing pathophysiological abnormalities such as diabetes and the pressure in the wound site substantially are known to cause deterioration to the wound healing (6,7). Impaired production and release of vascular endothelial growth factor (VEGF) at the wound site in diabetes have been defined as a key point for altered angiogenesis and subsequently impaired wound healing (8). Recent studies showed that statins have a crucial role in the regulation of angiogenesis (9). It was shown that simvastatin could increase VEGF synthesis and release at the wound site which is a crucial event for new blood vessels' production and subsequently ameliorates impaired wound healing in diabetic mice (10).

Worldwide 2–5% of patients with wound infection undergo surgical procedures each year. Also they are at a greater risk of impaired of wound healing due to change in physiological parameters following infection

international wound journal

such as angiogenesis and circulation to wound site (11,12).

Several treatment strategies have been evaluated to accelerate wound healing and prevention of deterioration to advanced stage of ulcers by prevention or treatment of wound infection (13), and it has been claimed that most of them had beneficial effects on wound healing (14–17).

In these days, statins because of diverse pleiotropic effects independent of their lipid-lowering activities potentially are considered a novel therapeutic modality for different pathological conditions such as psoriasis, sepsis, alopecia, wound healing and other inflammatory diseases (18,19).

The broad-spectrum pleiotropic effects of statins include anti-inflammatory (20), antioxidative (21), immunomodulatory (22,23), antibacterial activities (24) and improvement of microvascular function and reperfusion (18,25–28) and different animal models suggested that they have useful effects on wound-healing process (3,10,29).

Oral statins as same as other systemic medications can cause a number of adverse effects such as myopathy and liver problem (30), so topical delivery of statins may be a reasonable alternative to oral administration to prolong their valuable effects and reduce the incidence of adverse effects (31).

Considering the prognostic impact of statins on different aspects of wound-healing process, the application of statins in wound healing is rational and seems promising. Some research studies have focused to evaluate the effect of statins on the different phases of the healing process particularly inflammation and revascularisation phases. In this review, the effects of statins on wound healing in available clinical and non clinical studies have been evaluated.

METHODS

A literature search was performed using Scopus, PubMed, Medline, Cochrane central register of controlled trials and Cochrane database systematic reviews. Key words used as search terms were 'statins', 'lovastatin', 'atorvastatin', 'simvastatin', 'pravastatin', 'HMG-CoA', 'skin', 'cutaneous', 'skin lesion', 'skin damage', 'wound' and 'wound healing'. Any time limitation is not considered up to organising the review. All studies (experimental, quasi-experimental and clinical), which evaluated the effect of statins on wound healing as a main surrogate endpoint, were included. Improved wound-healing process was suggested in different animal (10,29,32–36) and human studies (37).

Experimental studies on the use of statins in wound healing

To date the beneficial effects of statins on improving wound healing have been evaluated in a number of experimental and clinical studies (Table 1). However, one study reported that fluvastatin can suppress non steroidal anti-inflammatory drug-induced ulcer formation because of its antioxidative activity in rats (38).

Effect of statin on the infected wound healing

The review identified that the first animal study that reported a beneficial effect of statins in wound healing was published by Rego *et al*. (32), who investigated the effect of topical treatment with simvastatin microemulsion on improvement of skin infected acute wound in rats. In this, animals were randomly allocated into two groups composed of seven rats in each group. A surgical procedure was performed to create a 1 cm^2 wound and after that wounds were contaminated with topical application of multibacterial solution which was prepared by fresh faeces of rats and saline. On day 2, 0·2 ml of topical simvastatin microemulsion (10 mg/ml) was administered daily on the infected wounds in the simvastatin group, whereas the wounds of control group were treated with saline solution once a day. Topical treatment was continued until the wounds healed in intervention group. Thereafter, histological and immunohistochemical properties of healed skin were evaluated. Samples of healed tissue for histopathology were evaluated by optical microscope and immunohistochemical staining. Also tumour necrosis factor (TNF)-α and interlukine-1β (IL-1β) were assessed. Bacteriological examination was performed on wound exudate on the fourth day of treatment. In comparison with saline solution therapy, administration of topical simvastatin microemulsion showed statistically significant improvement of wound healing based on histopathological

Key Points

- the broad-spectrum pleiotropic effects of statins include anti-inflammatory, antioxidative, immunomodulatory, antibacterial activities and improvement of microvascular function and reperfusion and different animal models suggested that they have useful effects on wound healing process
- oral statins as same as other systemic medications can cause a number of adverse effects such as myopathy and liver problem, so topical delivery of statins may be a reasonable alternative to oral administration to prolong their valuable effects and reduce the incidence of adverse effects
- in this review, the effects of statins on wound healing in available clinical and non clinical studies have been evaluated

Table 1 Animal and clinical studies of the wound-healing effect of statins

Study	Subjects/no.	Intervention	Control group	Duration of statin therapy	Effects of topical statin
Animal study of the wound-healing effect of statins					
Rego *et al.* (32)	Rats with open squared infected wound/14	Topically treated with 0·2 ml of simvastatin microemulsion (10 mg/ml) once a day	Topically treated with 0·2 ml saline solution daily	3 days	Histological, immunohistochemical and bacteriological properties were improved
Bitto *et al.* (10)	Diabetic mice with incision-induced wound/150	Simvastatin 5 mg/kg intraperitoneal daily	Solution of 30% dimethyl sulfoxide and 70% NaCl 0·9% (simvastatin vehicle)	12 days	Improve pattern of VEGF production and secretion and significantly ameliorate wound repair
Schiefelbein *et al.* (57)	Incision induced of skin and subcutaneous tissue/32	Simvastatin (40 mg/kg) intraperitoneally once a day	Treated intraperitoneally only with vehicle (ethanol and phosphate-buffered saline)	13 days	Significant decrease in VEGF protein expression and interfered with keratinocyte angiogenic and subsequently proliferation process during skin repair
Karadeniz Cakmak *et al.* (34)	Rats with intestinal anastomotic wound/32	Gavaged 10 mg/kg simvastatin once per day	Gavaged same volume of normal saline	7 days	Increased mechanical strength and collagen level in the anastomosis site
Toker *et al.* (29)	Streptozotocin-induced diabetic rat with diabetic foot wound/28	Topical atorvastatin 1% and 5%	Mixture of lanolin and vaseline	14 days	Higher healing rate, more reduction of wound surface area and better histological characteristics
Uygur *et al.* (35)	Ischaemic skin flap in rats/30	Group 1:5 mg/kg/day simvastatin intraperitoneally, group 2:1 mg/kg/day phosphate-buffered saline	No treatment was given to the control group	7 days	Higher surviving area and increased flap vascularity in group 1 compared to other groups and no evidence of necrosis in rats treated with simvastatin were seen
Holler *et al.* (36)	Radiation-induced skin lesion in mice/30	Four groups of eight wild-type mice (sham, sham + pravastatin 40 mg/kg/day in the food, 45 Gy, 45 Gy + pravastatin) and two groups of eight $eNOS^{-/-}$mice (45 Gy, 45 Gy + pravastatin)	Unirradiated mice considered to serve as control group	28 days	Decreasing leucocytes and endothelium interactions and limiting expression of inflammatory adhesion molecules and cell migration in tissue. eNOS plays a key role in pravastatin healing effect of skin lesion induced by a radiation.
Laing *et al.* (33)	Streptozotocin-induced diabetic rat with incision-induced wound/62	Gavaged pravastatin (0·4 mg/kg/day)	Gavaged sterile water of equivalent volume of intervention group	5 days	Collagen content and breaking strength increased, also significant elevation in nitric oxide level in wound fluid was noted
Clinical study of the wound-healing effect of statins					
Johansen *et al.* (37)	Diabetic patients with neuropathic diabetic foot ulcers < 4 months/13	10 mg atorvastatin in one group and 80 mg atorvastatin administered in another group	–	6 months	High-dose atorvastatin was associated with significant decrease in C-reactive protein and beneficial effects on lipids and ankle–arm blood pressure index compared with the low-dose atorvastatin group.

eNOS, endothelial NO synthase; VEGF, vascular endothelial growth factor.

and bacteriological examinations and also measurement of TNFα and IL-1β. The attenuation of inflammatory reactions and cytokine expression were showed by marked decrease in TNFα and IL-1β observed in the rats whose wounds were treated with simvastatin, and they were statistically significant. Topical simvastatin also decreased leucocyte infiltration and as a consequences reduced a leucocyte–endothelial cell interaction, which confirms the endothelium-protective effect of simvastatin suggested in some literature (39,40). One of the possible mechanisms of wound healing of infected skin was antibacterial effect of statins observed in this study. Acute and chronic wound healing may be delayed by acute inflammatory response of bacterial infection. Recently, the antibacterial effect of statins was investigated in different studies (25,41–45). There is some evidence to suggest that statins may be helpful for reducing bacterial burden, improving epithelialisation and wound healing (25,41–45). Although these studies showed useful effects of statins on healing of infected wound, but future studies should be conducted to show the antibicrobial effect of statins on different pathological conditions such as various soft tissue infections.

Effect of statin on the anastomotic wound healing

Karadeniz Cakmak *et al*. (34) investigated the effect of statins in anastomic wound healing by conducting an experimental study using an animal model, the potential benefit of 10 mg/kg simvastatin by mouth with gavage catheter daily was investigated on wound complications such as intra-abdominal abscesses formation and leakage at anastomotic site, and bursting pressure and hydroxyroline content were also measured to assess mechanical and biochemical healing, respectively (34). In addition, tissue granulation, local inflammatory response and histological changes of anastomotic wound healing were assessed according the certain scale (34), and mucosal ischaemia was determined by Chiu scale (46). Macroscopic healing was assessed by two surgeons and graded according to the specific scale (47). A total of 32 rats were randomly allocated in simvastatin ($n = 16$) and control (tap water) ($n = 16$) groups, and then anastomosis intervention started after 1 week and maintained during the study period. Finally, healing parameters were investigated in third and seventh post-treatment days. Simvastatin treatment leads to better histopathological features in terms of increased reepithelialisation, decreased granuloma formation and inflammatory infiltration to muscle layer and reduced ischaemic necrosis. Also simvastatin administration leads to a significantly higher mechanical and biochemical healing than control group, while neither anastomotic leakage nor septic complications were detected in both the study and control groups (34).

Effect of statin on the diabetic wound healing

Diabetes mellitus and its complications are common problems throughout the world (48). Healing defect of diabetic wound is prevalent between these patients and results in high economic burden for health care organisations. Several interventions have been initiated to improve wound healing in diabetic patients such as wound dressing (49), honey as a dressing solution (50) and topical antimicrobial therapies (51). On the basis of the available evidences that showed beneficial effects of statins on wound healing (29,37), it was proposed that statins may have beneficial effects on the management of diabetic foot wound (29,37). In 2008, Bitto *et al*. evaluated the intraperitoneal efficacy of simvastatin in diabetes-related impaired wound healing. This study was conducted on 150 mice in total, and 10 animals were recruited in each group (diabetic or normoglycaemia, simvastatin or vehicle treated or VEGF neutralising antibody pretreated) in each time point (3, 6 and 12 days). Simvastatin (5 mg/kg) or its vehicle was given intraperitoneal daily in each group until time point (3, 6 and 12 days), thereafter animals in each group were killed and wounds were evaluated by histology, breaking strength and molecular analysis. VEGF mRNA was measured by Western blot analysis, healing process was assessed histologically, and histological score was calculated to give a quantification of these parameters (52); wound breaking strength was also evaluated by using a calibrated tensometer (53) and angiogenesis was measured by CD31 immunostaining. An additional group of mice were treated with anti-VEGF monoclonal antibody 1 week before starting simvastatin and killed in certain time (3, 6 and 12 days) to

Key Points

- this study clearly showed that simvastatin was able to improve the pattern of VEGF production and secretion and significantly ameliorate wound repair by measurement of VEGF mRNA, protein expression and enhanced nitric oxide (NO) wound content
- beneficial effect of simvastatin with passive immunisation by anti- VEGF monoclonal antibody completely cancelled the beneficial effects of simvastatin on wound healing, so it is suggested that VEGF plays a main role in simvastatin effect in wound-healing process
- although some concerns exist that endothelial regeneration resulting from VEGF may increase tumour growth, there is not any document about tumour growth in post-marketing surveillance studies
- this study showed simvastatin only inhibit insulin-induced translation of VEGF mRNA and also, interfered with proliferation of cultured keratinocytes
- according to the result of this study, topical administration of atorvastatin had significant higher wound-healing rates than placebo at days 7 and 14
- according to the result of this study, collagen content and breaking strength increased on day 10 post-wounding, and there was a significant elevation in NO level in the wound fluid of pravastatin group
- so the result of this study showed other mechanisms of statins which may be useful in wound healing such as increased wound breaking strength and elevated NO levels

clarify molecular relationship between wound healing and VEGF in diabetes. This study clearly showed that simvastatin was able to improve the pattern of VEGF production and secretion and significantly ameliorate wound repair by measurement of VEGF mRNA, protein expression and enhanced nitric oxide (NO) wound content. Beneficial effect of simvastatin with passive immunisation by anti-VEGF monoclonal antibody completely cancelled the beneficial effects of simvastatin on wound healing, so it is suggested that VEGF plays a main role in simvastatin effect in wound-healing process (10,54,55). Although some concerns exist that endothelial regeneration resulting from VEGF may increase tumour growth, there is not any document about tumour growth in post-marketing surveillance studies (56).

In contrast to the previous study, in the same year, another in vivo study suggested that simvastatin can decrease in VEGF protein expression, interfere with keratinocyte angiogenic and proliferation process during skin repair (57). However, wound healing outcome was not reported in this study. In this evaluation, wounding of mice were performed by excising the skin and subcutaneous tissue in six different sites and then interventions were made by simvastatin (40 mg/kg) intraperitoneally once a day in case group and vehicle (ethanol and phosphate-buffered saline) in control group. Specimens were taken in 1, 3, 5, 6, 7 and 13 days after wounding and were analysed for different parameters to assess the effect of HMG-CoA reductase expression on keratinocyte angiogenic and proliferation during wound healing (57). For each time point, VEGF mRNA analysis was conducted for 16 wounds (4 wounds from four animals), also VEGF protein analysis of 8 wounds (2 wounds from 4 animals) were performed and 4 unwounded animals were considered as control. This study showed simvastatin only inhibit insulin-induced translation of VEGF mRNA and also, interfered with proliferation of cultured keratinocytes. Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by simvastatin in wounded mice with acutely regenerating tissue was paralleled with loss of VEGF protein expression and interferences of normal proliferation of keratinocytes during skin repair.

Subsequently, Toker *et al*. (29) evaluated the efficacy of topical atorvastatin on diabetic foot healing in using 56 streptozotocin-induced diabetic rats in eight groups and compared wound-healing rates between topical Atorvastatin (1% and 5%), placebo (mixture of lanolin – vaseline) and untreated groups at days 7 and 14. First and second groups received no treatment for 7 and 14 days, respectively, third and fourth groups treated with placebo for 7 and 14 days, respectively, topical formulation if atorvastatin 1% was used in fifth and sixth groups for 7 and 14 days, respectively, and atorvastatin 5% was administered for 7 and 14 days in seventh and eighth groups, respectively. In addition, healing was assessed according to wound size measurement and histopathological study on the 7 and 14 days. Wound healing was evaluated according to wound surface area reduction with a stereomicroscope and photograph. Healing rate was expressed based on percent of healed skin area. Other healing criteria were histological characteristics such as regeneration of epidermis and dermis, granulation and angiogenesis. According to the result of this study, topical administration of atorvastatin had significant higher wound-healing rates than placebo at days 7 and 14. However, there were not any significant differences in wound healing between 1% and 5% topical atorvastatin in 7 and 14 days after therapy, so duration of topical atorvastatin administration was more correlated with drug efficacy when compared with the dosage of atorvastatin (29).

Another recent investigation has reported NO as a potential target for the effect of pravastatin on experimental diabetic wound healing (33). This novel mediator, NO, has been proposed to play different roles during diabetic foot wound healing, which is related to stimulatory effect on fibroblast activity or indirect effects such as vasodilatation and cytokine expression (58–60). In this study, 70 diabetic rats were assigned to two groups, one group treated with gavaged pravastatin (0·4 mg/kg) for five consecutive days, and the other group received an equivalent volume of sterile water. According to the result of this study, collagen content and breaking strength increased on day 10 post-wounding, and there was a significant elevation in NO level in the wound fluid of pravastatin group (33). So the result of this study showed other mechanisms

of statins which may be useful in wound healing such as increased wound breaking strength and elevated NO levels.

Effect of statin on the ischaemic skin flap healing

Simvastatin seems to have a positive therapeutic potential on flap survival because of its upregulation of thrombomodulin from the surface of vascular endothelial, increased dermal blood flow and decreased microthrombus formation properties (35). In an experimental study, the beneficial effect of simvastatin was assessed in the ischaemic skin flap model. The sample included 30 rats divided into three different groups. Group 1 received 5 mg/kg/day simvastatin, intraperitoneally, group 2 received 1 mg/kg/day phosphate-buffered saline and no treatment was given to control group. Thereafter, the effect of simvastatin was evaluated by comparison of flap survival rate, blood flow and vascularity showed by microangiography between these three groups. Higher surviving area and increased flap vascularity in group 1 compared to other groups and no evidence of necrosis in rats that were treated with simvastatin suggested simvastatin contribution to flap survival (mean necrotic rates of flaps reported 23·7% in group 1 which was significantly lower in comparison of group 2 and control group that reported 45·35% and 45·56%, respectively) (35). Sensitivity of the techniques and subjective assessment that were applied for evaluation of the endothelial parameters are limitations of this study.

Effect of statin on the healing of radiation-induced skin lesion

Useful effects of pravastatin on healing of radiation-induced skin lesions were reported following maintenance of endothelial function by their anti-inflammatory and antioxidant activities (36). Radiation-induced inflammatory responses and endothelial dysfunction by limiting NO availability was induced in two different mice groups: wild-type mice and endothelial NO synthase (eNOS) mice. Mice were randomly allocated in four groups of eight wild-type mice (unirradiated, unirradiated + pravastatin, irradiated and irradiated + pravastatin) and two groups of eight eNOS mice (irradiated and irradiated + pravastatin) and they were followed up for 28 days. Pravastatin was administered orally in a dose of 40 mg/kg/day in the mice food. The results of this study showed useful pravastatin therapeutic effects on preventing skin damage by decreasing leucocytes and endothelium interactions, limiting expression of inflammatory adhesion molecules and cell migration in mice's tissue. In addition, it seems that eNOS plays a key role in pravastatin healing effect of skin lesion induced by a radiation (36).

Clinical use of atorvastatin in wound healing in human studies

Effect of statin on the diabetic wound healing

Parallel to the findings of conducted experimental studies, Johansen *et al*. (37) investigated the effects of an oral statin in diabetic foot ulcer (DFU) healing process in a pilot randomised trial in humans. Six patients treated with 10 mg atorvastatin orally in one group and 80 mg atorvastatin administered in seven patients in another group in addition to conventional management of DFU for 6 months. There were no significant differences between two groups with regard to diabetic control and complications, concomitant medications including oral hypoglycaemic agents, insulin and antiplatelet therapy. Administration of high-dose atorvastatin was associated with significant decrease in C-reactive protein. In addition, this study showed beneficial effects of high-dose atorvastatin on lipids and ankle-brachial blood pressure index compared with the low-dose atorvastatin group (37). However, it seems this study is too small to have a clinical interpretation and further clinical trial will be needed.

Another human study showed that short-term oral atorvastatin treatment could increase circulating endothelial precursors in patients with systemic sclerosis in a pilot study (61), and promote angiogenesis in vivo in animal model of ischaemia (9,62–64).

CONCLUSION

In summary, a total of eight animal studies and one clinical trial have been found that evaluated the effect of statins on wound healing. Also inhibitory effect of fluvastatin on ulcer formation induced by non steroidal anti-inflammatory drug was discussed in another

Key Points

- in summary, a total of eight animal studies and one clinical trial have been found that evaluated the effect of statins on wound healing
- the results from all of these studies consistently showed that the use of statins produced a significant improvement of wound healing in different types of wounds and in both oral and topical administration and also in short- and long-term follow up
- healing outcome was not evaluated in this study, while other reported studies showed better wound-healing outcome with statin therapy
- topical delivery through local tissue area may be an alternative to oral administration to reduce the incidence of adverse reactions and sustain effects for longer periods
- further study should be designed to determine appropriate route of statin administration for wound care
- a review of the literature showed that dose and type of statin can affect the outcome
- future studies should be carried out by focusing on potential benefit of another statins such as lovastatin, fluvastatin and rosuvastatin on wound healing
- whether statins are effective for improving wound healing in clinical setting, and whether long-term statin therapy is appropriate for delaying or prevention of wound exacerbation, are questions remained to be answered in large-scale clinical trials
- recent progress in the potential benefit of statin therapy on wound healing warrants further investigations on evaluating the effect of statins on the other type of wounds such as pressure ulcers or venous leg ulcers
- although pleiotropic effects of statins can target multiple pathophysiological conditions including wound-healing pathogenesis, these results need to be confirmed by high-quality controlled clinical trial before recommending to be used in clinical practice

study in rats (38). The results from all of these studies consistently showed that the use of statins produced a significant improvement of wound healing in different types of wounds and in both oral and topical administration and also in short- and long-term follow-up (10,29,32–37). Only in one study, simvastatin therapy was related to disturbance of normal proliferation during skin repair as a result of abolished VEGF protein release (57). Healing outcome was not evaluated in this study, while other reported studies showed better wound-healing outcome with statin therapy.

Topical delivery through local tissue area may be an alternative to oral administration to reduce the incidence of adverse reactions and sustain effects for longer periods. However, diffusion coefficient of local statins must be evaluated because transdermal penetration of compounds through the skin may be insufficient due to low permeability (physicochemical properties of the compound) and partition ability. Further study should be designed to determine appropriate route of statin administration for wound care.

A review of the literature showed that dose and type of statin can affect the outcome. However, the findings of described studies showed wound-healing effect of simvastatin, atorvastatin and pravastatin. Future studies should be carried out by focusing on potential benefit of another statins such as lovastatin, fluvastatin and rosuvastatin on wound healing.

Evidence of the potential beneficial effect of statins on wound healing is mostly based on animal studies with small sample sizes and short-term follow-up. Whether statins are effective for improving wound healing in clinical setting, and whether long-term statin therapy is appropriate for delaying or prevention of wound exacerbation, are questions remained to be answered in large-scale clinical trials. Three studies showed improvement of endothelial function especially by upregulating NO synthase (33,36), improving pattern of VEGF production (10) and reducing oxidative stress as a main role of statin during wound-healing process independently of their well-known lipid-lowering action (32). Also antibacterial, improving epithelialisation and increasing mechanical strength were reported to have potential effect on wound healing during statin therapy (10,34). Evidence-based studies are necessary to confirm pleiotropic effects of statins and their probable clinical benefits on wound-healing relationship. Although statins showed beneficial effects on different types of wounds such as infected, anastomotic, ischaemic and diabetic wounds in animal studies, more studies are essential to compare the healing effect of statins on different wounds. Recent progress in the potential benefit of statin therapy on wound healing warrants further investigations on evaluating the effect of statins on the other type of wounds such as pressure ulcers or venous leg ulcers.

Future perspective

Chronic wounds healing such as DFUs and pressure sores are usual problem for patients and health care workers. Management of these wounds or prevention of progression to advanced stages is one of the most important strategies for health care providers. Although pleiotropic effects of statins can target multiple pathophysiological conditions including wound-healing pathogenesis, these results need to be confirmed by high-quality controlled clinical trial before recommending to be used in clinical practice.

ACKNOWLEDGEMENT

This review is not supported financially and authors declare no conflict of interest.

REFERENCES

1 Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. J Clin Invest 2007;117(5):1219–22.
2 Pastar I, Stojadinovic O, Tomic-Canic M. Role of keratinocytes in healing of chronic wounds. Surg Technol Int 2008;17:105–12.
3 Vukelic S, Stojadinovic O, Pastar I, Vouthounis C, Krzyzanowska A, Das S, Samuels HH, Tomic-Canic M. Farnesyl pyrophosphate inhibits epithelialization and wound healing through the glucocorticoid receptor. J Biol Chem 2010;285(3):1980–8.
4 Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. Journal of Investigative Dermatology. 2007;127(3):514–25.
5 Redd MJ, Cooper L, Wood W, Stramer B, Martin P. Wound healing and inflammation: embryos reveal the way to perfect repair. Philos Trans R Soc Lond B Biol Sci. 2004;359(1445):777–84.
6 McDermott-Scales L, Cowman S, Gethin G. Prevalence of wounds in a community care setting in Ireland. J Wound Care. 2009;18(10):405–17
7 Bours GJJW, Halfens RJG, Abu Saad HH, Grol RTPM. Prevalence, prevention, and treatment

of pressure ulcers: descriptive study in 89 institutions in the Netherlands. Research in nursing & health. 2002;25(2):99–110.
8 Galeano M, Deodato B, Altavilla D, Cucinotta D, Arsic N, Marini H, Torre V, Giacca M, Squadrito F. Adeno-associated viral vector-mediated human vascular endothelial growth factor gene transfer stimulates angiogenesis and wound healing in the genetically diabetic mouse. Diabetologia. 2003;46(4):546–55.
9 Kureishi Y, Luo Z, Shiojima I, Bialik A, Fulton D, Lefer DJ, Sessa WC, Walsh K. The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. Nat Med. 2000; 6(9):1004–10.
10 Bitto A, Minutoli L, Altavilla D, Polito F, Fiumara T, Marini H, Galeano M, Calò M, Lo Cascio P, Bonaiuto M, Migliorato A, Caputi AP, Squadrito F. Simvastatin enhances VEGF production and ameliorates impaired wound healing in experimental diabetes. Pharmacological Research. 2008;57(2):159–69.
11 Pishori T, Siddiqui AR, Ahmed M. Surgical wound infection surveillance in general surgery procedures at a teaching hospital in Pakistan. Am J Infect Control. 2003;31(5):296–301.
12 Narong MN, Thongpiyapoom S, Thaikul N, Jamulitrat S, Kasatpibal N. Surgical site infections in patients undergoing major operations in a university hospital: Using standardized infection ratio as a benchmarking tool* 1. Am J Infect Control. 2003;31(5):274–9.
13 Burns JL, Mancoll JS, Phillips LG. Impairments to wound healing. Clin Plast Surg 2003;30(1):47–56.
14 Garros IC, Campos ACL, Tâmbara EM, Tenório SB, Torres OJM, Agulham MÂ, Araújo AC, Santis-Isolan PM, Oliveira RM, Arruda EC.. Extract from Passiflora edulis on the healing of open wounds in rats: morphometric and histological study. Acta Cir Bras. 2006;21:55–65.
15 Santos MFS, Czeczko NG, Nassif PAN, Ribas-Filho JM, Alencar BLF, Malafaia O, Ribas CA, Trautwein VM, Henriques GS, Maia JM, Bittencourt RC. Evaluation of the use of raw extract of Jatropha gossypiifolia L. in the healing process of skin wounds in rats. Acta Cir Bras. 2006;21:2–7.
16 Nunes Jr JAT, Ribas-Filho JM, Malafaia O, Czeczko NG, Inácio CM, Negrão AW, Lucena PL, Moreira H, Wagenfuhr J Jr, Cruz Jde J. Evaluation of the hydro-alcoholic Schinus terebinthifolius Raddi (Aroeira) extract in the healing process of the alba linea in rats. Acta Cir Bras. 2006;21:8–15.
17 Martins NLP, Malafaia O, Ribas-Filho JM, Heibel M, Baldez RN, Vasconcelos PRL, Moreira H, Mazza M, Nassif PA, Wallbach TZ. Healing process in cutaneous surgical wounds in rats under the influence of Orbignya phalerata aqueous extract. Acta Cir Bras. 2006;21:66–75.
18 Corsonello A, Garasto S, Abbatecola AM, Rose G, Passarino G, Mazzei B, Pranno L, Guffanti EE, Bustacchini S, Lattanzio F. Targeting inflammation to slow or delay functional decline: where are we? Biogerontology. 2010;11(5):603–14.
19 Libby P OY, Rocha VZ, Folco E. Inflammation in atherosclerosis: transition from theory to practice. Circ J 2010;74(2):213–20.
20 Diomede L, Albani D, Sottocorno M, Donati MB, Bianchi M, Fruscella P, Salmona M. In vivo anti-inflammatory effect of statins is mediated by nonsterol mevalonate products. Arteriosclerosis, thrombosis, and vascular biology. 2001;21(8): 1327–32.
21 Adam O, Laufs U. Antioxidative effects of statins. Archives of toxicology. 2008;82(12):885–92.
22 Blanco-Colio LM, Tuñón J, Martín-Ventura JL, Egido J. Anti-inflammatory and immunomodulatory effects of statins. Kidney international. 2003;63(1):12–23.
23 Mach F. Statins as immunomodulatory agents. Circulation. 2004;109 (21 Suppl 1):II15–7.
24 Jerwood S, Cohen J. Unexpected antimicrobial effect of statins. Journal of antimicrobial chemotherapy. 2008;61(2):362–4.
25 Merx MW, Liehn EA, Janssens U, Lutticken R, Schrader J, Hanrath P, Weber C. HMG-CoA reductase inhibitor simvastatin profoundly improves survival in a murine model of sepsis. Circulation. 2004;109(21):2560–5.
26 Ginter E, Simko V. Statins: the drugs for the 21st century? Bratisl Lek Listy. 2009;110(10):664–8.
27 Pruefer D, Makowski J, Schnell M, Buerke U, Dahm M, Oelert H, Sibelius U, Grandel U, Grimminger F, Seeger W, Meyer J, Darius H, Buerke M. Simvastatin inhibits inflammatory properties of Staphylococcus aureus {alpha}-toxin. Circulation. 2002;106(16):2104–10.
28 Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. *Nat Me*. 2000;6(12):1399–402.
29 Toker S, Gulcan E, Çayc MK, Olgun EG, Erbilen E, Özay Y. Topical atorvastatin in the treatment of diabetic wounds. Am J Med Sci 2009;338(3):201–4
30 Katz U, Zandman-Goddard G. Drug-induced lupus: an update. Autoimmunity Reviews. 2010;10(1): 46–50.
31 Yonessi M, Saeedi M. A double-blind placebo-controlled evaluation of the effect of topical sildenafil on erectile dysfunction. JOURNAL OF APPLIED RESEARCH 2005;5(2):289–94.
32 Rego ACM, Araújo Filho I, Damasceno BPGL, Egito EST, Silveira IA, Brandão-Neto J, Medeiros AC. Simvastatin improves the healing of infected skin wounds of rats. Acta Cirúrgica Brasileira. 2007;22(1):57–63.
33 Laing T, Hanson R, Chan F, Bouchier-Hayes D. Effect of pravastatin on experimental diabetic wound healing. J Surg Res. 2010;161(2):336–40.
34 Karadeniz Cakmak G, Irkorucu O, Ucan B, Emre A, Bahadir B, Demirtas C, Tascilar O, Karakaya K, Acikgoz S, Kertis G, Ankarali H, Pasaoglu H, Comert M. Simvastatin improves wound strength after intestinal anastomosis in the rat. J Gastrointest Surg 2009;13(9):1707–16.
35 Uygur F, Noyan N, Hahaolu A. The effect of simvastatin on the survival of ischaemic skin flap: An experimental study in rats. J Plast Reconstr Aesthet Surg. 2009;63(10):1723–32.

36 Holler V, Buard V, Gaugler MH, Guipaud O, Baudelin C, Sache A, Perez Mdel R, Squiban C, Tamarat R, Milliat F, Benderitter M. Pravastatin limits radiation-induced vascular dysfunction in the skin. Journal of Investigative Dermatology. 2009;129(5):1280–91.
37 Johansen OE BK, Jørgensen AP, Orvik E, Sørgård B, Torjussen BR, Ueland T, Aukrust P, Gullestad L. Diabetic foot ulcer burden may be modified by high dose atorvastatin: A 6 month randomized controlled pilot trial. J Diabetes. 2009;1(3):182–7.
38 Hagiwara M, Kataoka K, Arimochi H, Kuwahara T, Nakayama H, Ohnishi Y. Inhibitory effect of fluvastatin on ileal ulcer formation in rats induced by nonsteroidal antiinflammatory drug. World J Gastroenterol. 2005;11(7):1040–3.
39 Simko F, Matuskova J, Luptak I, Krajcirovicova K, Kucharska J, Gvozdjakova A, Babal P, Pechanova O. Effect of simvastatin on remodeling of the left ventricle and aorta in L-NAME-induced hypertension. Life sciences. 2004;74(10):1211–24.
40 Pruefer D, Scalia R, Lefer AM. Simvastatin inhibits leukocyte-endothelial cell interactions and protects against inflammatory processes in normocholesterolemic rats. Arteriosclerosis, thrombosis, and vascular biology. 1999;19(12):2894–900.
41 Tleyjeh IM, Kashour T, Hakim FA, Zimmerman VA, Erwin PJ, Sutton AJ, Ibrahim T. Statins for the Prevention and Treatment of Infections. Arch Intern Med. 2009;169(18):1658–67.
42 Dobesh PP, Klepser DG, McGuire TR, Morgan CW, Olsen KM. Reduction in mortality associated with statin therapy in patients with severe sepsis. Pharmacotherapy. 2009;29(6):621–30.
43 Donnino MW, Cocchi MN, Howell M, Clardy P, Talmor D, Cataldo L, Chase M, Al-Marshad A, Ngo L, Shapiro NI. Statin therapy is associated with decreased mortality in patients with infection. Acad Emerg Med 2009;16(3):230–4.
44 Jerwood S, Cohen J. Unexpected antimicrobial effect of statins. J Antimicrob Chemother 2008;61(2):362–4.
45 Merx MW, Liehn EA, Graf J, van de Sandt A, Schaltenbrand M, Schrader J, Hanrath P, Weber C. Statin treatment after onset of sepsis in a murine model improves survival. Circulation. 2005;112(1):117–24.
46 Chiu CJ, McArdle AH, Brown R, Scott HJ, Gurd FN. Intestinal mucosal lesion in low-flow states: I. A morphological, hemodynamic, and metabolic reappraisal. Archives of Surgery. 1970;101(4):478.
47 Hulka J, Omran K, Berger G. Classification of adnexal adhesions: a proposal and evaluation of its prognostic value. Fertility and sterility. 1978;30(6):661–5
48 Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes research and clinical practice. 2010;87(1):4–14.
49 Kordestani S, Shahrezaee M, Tahmasebi M, Hajimahmodi H, Haji Ghasemali D, Abyaneh M. A randomised controlled trial on the effectiveness of an advanced wound dressing used in Iran. J Wound Care. 2008;17(7):323–7.
50 Shukrimi A, Sulaiman A, Halim A, Azril A. A comparative study between honey and povidone iodine as dressing solution for Wagner type II diabetic foot ulcers. Med J Malaysia. 2008;63(1):44–6.
51 Lipsky BA, Holroyd KJ, Zasloff M. Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: a randomized, controlled, double-blinded, multicenter trial of pexiganan cream. Clinical infectious diseases. 2008;47(12):1537–45
52 Altavilla D, Saitta A, Cucinotta D, Galeano M, Deodato B, Colonna M, Deodato B, Colonna M, Torre V, Russo G, Sardella A, Urna G, Campo GM, Cavallari V, Squadrito G, Squadrito F. Inhibition of lipid peroxidation restores impaired vascular endothelial growth factor expression and stimulates wound healing and angiogenesis in the genetically diabetic mouse. Diabetes. 2001;50(3):667–74
53 Pierce GF, Mustoe TA, Senior RM, Reed J, Griffin GL, Thomason A, Deuel TF. In vivo incisional wound healing augmented by platelet-derived growth factor and recombinant c-sis gene homodimeric proteins. The Journal of experimental medicine. 1988;167(3):974–87.
54 Matsuno H, Takei M, Hayashi H, Nakajima K, Ishisaki A, Kozawa O. Simvastatin enhances the regeneration of endothelial cells via VEGF secretion in injured arteries. Journal of cardiovascular pharmacology. 2004;43(3):333–40.
55 Wu H, Lu D, Jiang H, Xiong Y, Qu C, Li B, Mahmood A, Zhou D, Chopp M. Simvastatin-mediated upregulation of VEGF and BDNF, activation of the PI3K/Akt pathway, and increase of neurogenesis are associated with therapeutic improvement after traumatic brain injury. Journal of neurotrauma. 2008;25(2):130–9.
56 Ungvari Z, Pacher P, Csiszar A. Can simvastatin promote tumor growth by inducing angiogenesis similar to VEGF? Med Hypotheses. 2002;58(1):85–6.
57 Schiefelbein D, Goren I, Fisslthaler B, Schmidt H, Geisslinger G, Pfeilschifter J, Frank S. Biphasic regulation of HMG-CoA reductase expression and activity during wound healing and its functional role in the control of keratinocyte angiogenic and proliferative responses. Journal of Biological Chemistry. 2008;283(22):5479–15490.
58 Rizk M, Witte MB, Barbul A. Nitric oxide and wound healing. World J Surg. 2004;28(3):301–6.
59 Schwentker A, Billiar TR. Nitric oxide and wound repair. Surg Clin North Am. 2003;83(3):521–30.
60 Laufs U. Beyond lipid-lowering: effects of statins on endothelial nitric oxide. Eur J Clin Pharmacol. 2003;58(11):719–31.
61 Kuwana M, Kaburaki J, Okazaki Y, Yasuoka H, Kawakami Y, Ikeda Y. Increase in circulating endothelial precursors by atorvastatin in patients with systemic sclerosis. Arthritis Rheum. 2006;54(6):1946–51.
62 Dimmeler S, Aicher A, Vasa M, Mildner-Rihm C, Adler K, Tiemann M, Rütten H, Fichtlscherer S,

Martin H, Zeiher AM. HMG-CoA reductase inhibitors (statins) increase endothelial progenitor cells via the PI 3-kinase/Akt pathway. J Clin Invest. 2001;108(3):391–7.

63 Llevadot J, Murasawa S, Kureishi Y, Uchida S, Masuda H, Kawamoto A, Walsh K, Isner JM, Asahara T. HMG-CoA reductase inhibitor mobilizes bone marrow-derived endothelial progenitor cells. J Clin Invest. 2001;108(3):399–405.

64 Walter DH, Rittig K, Bahlmann FH, Kirchmair R, Silver M, Murayama T, Nishimura H, Losordo DW, Asahara T, Isner JM. Statin therapy accelerates reendothelialization: a novel effect involving mobilization and incorporation of bone marrow-derived endothelial progenitor cells. Circulation. 2002;105(25):3017–24.